REMARKS

Claims 1, 2, 4-6, and 43-46 are pending in the application. Claims 1, 2, 4-6, and 43-46 stand rejected. Claims 1, 2, 6, 43, 44, and 45 have been amended. Claim 43 has been withdrawn due to the election of species requirement. Reconsideration and allowance of Claims 1, 2, 4-6, and 43-46 is respectfully requested.

The Objection to Claim 6

Claim 6 has been amended to recite "said co-segregation analysis comprises restriction fragment length polymorphism analysis" as suggested by the Examiner. Accordingly, removal of this objection is respectfully requested.

The Rejection of Claims 1-2, 4-6, and 43-46 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-2, 4-6, and 43-46 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner has taken the view that clarification is required because the terms "ataxia" and "ataxic neurological disease" are not synonyms and differ in scope.

In order to facilitate prosecution, Claim 1, from which Claims 2, 4-6, and 43-46 depend, and Claim 45 have been amended to recite "adult onset cerebellar ataxia." Support for this amendment is found throughout the specification as filed, for example, page 2, lines 6-9, page 3, lines 28-31, page 6, lines 27-32, and page 23, line 21-23.

With regard to the Examiner's rejection of Claims 1, 2, and 43-44, Claim 2 has been amended to recite "wherein the first nucleic acid sequence from said first human subject is determined by amplification of at least a portion of the human protein kinase C gamma gene from genomic DNA." Claim 44 has been amended to depend from Claim 1 and now recites

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"wherein the first nucleic acid sequence comprises exon 4 of the human protein kinase C gamma gene."

Claim 43, which depends from generic Claim 1, has been withdrawn due to the election of species requirement. Claim 43 has been amended to depend from Claim 1 and now recites "wherein the first nucleic acid sequence is a coding region of the human protein kinase C gamma gene selected from the group consisting of exon 1, exon 2 . . . and exon 18."

Claims 43-44 have been amended to delete the particular ranges of nucleotides found in SEQ ID NO:3 in parentheses.

Accordingly, removal of this ground of rejection is respectfully requested.

The Rejection of Claims 1-2, 4-6, and 43-46 Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 1-2, 4-6, and 43-46 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner acknowledges that the specification is enabling for a method of diagnosing a predisposition to cerebellar ataxia in a human subject by detecting the presence of H101Y in the protein kinase C gamma gene of a human subject. However, the Examiner has taken the position that the specification is not enabling for a screen method in which any type of sequence difference with respect to SEQ ID NO:3 in any human subject exhibiting any type of ataxia may be identified and confirmed as being associated with ataxia by simply determining that the difference is present in at least two ("a plurality") subjects exhibiting ataxia and absent in at least two subjects ("a plurality") without ataxia.

Although the Examiner acknowledges that given the high level of skill in the relevant art area, it is clearly within the ability of such an artisan to identify differences between various sequences, that one of skill could clearly practice the disclosed RFLP analysis, and that one of skill could clearly practice the various techniques of co-segregation analysis cited in the

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application, the Examiner has taken the position that it is unpredictable as to whether one of skill in the art could practice the invention of the instant claims.

While not acquiescing to the Examiner's position, but in order to facilitate prosecution, as noted above, Claim 1, from which Claims 2, 4-6, and 43-46 depend, and Claim 45 have been amended to recite "adult onset cerebellar ataxia." Support for this amendment is found throughout the specification as filed, for example, page 2, lines 6-9, page 3, lines 28-31, page 6, lines 27-32, and page 23, lines 21-23.

Claim 1 has also been amended to recite at step (b): "identifying a difference between the first nucleic acid sequence from the first human subject exhibiting adult onset cerebellar ataxia and SEQ ID NO:3, wherein the difference alters the amino acid sequence encoded by the human protein kinase C gamma gene." Support for this amendment is found throughout the specification as filed, for example at page 6, lines 23-32, page 11, lines 11-29, TABLE 3, and page 18, lines 2-9.

As noted above, Claim 44 has been amended to clarify that the first nucleic acid sequence comprises exon 4 of the human protein kinase C gamma gene, which is compared to SEQ ID NO:3.

1. The Examiner Has Failed to Establish a Prima Facie Case of Non-Enablement

As an initial matter, it is submitted that the Examiner has not met the required burden of establishing a reasonable basis to question the enablement provided in the specification for the claimed invention.

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C.§ 112, first paragraph, unless there is a reasons to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

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M.P.E.P. § 2164.04, citing *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971) (emphasis in the original). "[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is consistent with the contested statement." *Id.* at 224, 169 U.S.P.Q. at 370.

It is submitted that Claims 1, 2, 4-6, and 44-46, as amended, are enabled by the specification as filed in view of the knowledge of the skilled artisan at the time the application was filed.

The Examiner has taken the position that the specification is not enabling for a screen method in which any type of sequence difference with respect to SEQ ID NO:3 in any human subject exhibiting any type of ataxia may be identified and confirmed as being associated with ataxia by simply determining that the difference is present in at least two ("a plurality") subjects exhibiting ataxia and absent in at least two subjects ("a plurality") without ataxia. The Examiner has also noted that the list of mutations in TABLE 3 includes a variety of silent mutations.

In this regard, it is noted that Claim 1, as amended, specifies the identification of a difference between a first nucleic acid sequence of a human protein kinase C gamma gene from a first human subject exhibiting *adult onset cerebellar ataxia* and *SEQ ID NO:3*, wherein the difference *alters the amino acid sequence* encoded by the human protein kinase C gamma gene; and confirming that the difference identified is a genetic mutation associated with adult onset cerebellar ataxia by co-segregation analysis in human subjects.

As stated in the specification, the term 'genetic mutation' is an alteration of the wild-type protein kinase C gamma (PRKCG) sequence deposited in GENBANK, provided as SEQ ID NO:3 that is not a recognized polymorphism (i.e., has a population frequency less than 1% in mammalian control subjects of the same species that do not exhibit ataxia).

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Contrary to the Examiner's assertion, the specification does provide evidence of a statistical association between the presence of mutations identified in PRKCG and adult-onset cerebellar ataxia. For example, as described in Example 1, in a group of 24 subjects that were members of a four generation family with some of the members suffering from adult onset cerebellar ataxia, the mutation H101Y in PRKCG was found in ten members of the family and the H101Y mutation segregated with the presence of ataxia in all ten cases. In contrast, the H101Y mutation was not found in 192 normal controls (384 chromosomes). Specification at page 23, line 16, to page 25, line 21.

2. *Adequate Guidance Is Provided in the Specification for One of Skill in the Art to Practice the Claimed Method Without Undue Experimentation*

The Examiner has taken the view that the specification does not provide adequate guidance for one skilled in the art on how to practice the full scope of the instant method without undue experimentation. In this regard, it is noted that the Examiner acknowledges that the specification discloses:

> a particular mutation, the 'C to T transition in nucleotide 301 (H101Y),' that was identified by screening the protein kinase C gamma gene in healthy and diseased populations of human subjects, and which is clearly associated with a particular type of ataxia (the 'unexplained cerebellar ataxia' discussed in Example 1) in a particular type of subject (humans), such that one of skill in the art could clearly practice methods of e.g., diagnosing predisposition to this type of ataxia in a human subject by detecting the presence of this particular alteration in the protein kinase C gamma gene of the human subject.

(See page 5 of non-final Office Action mailed February 15, 2007.) The Examiner further acknowledges:

> [g]iven the high level of skill of one skilled in the art relevant to the claimed invention, it is clearly within the ability of such an artisan to conduct screening methods, e.g., employing samples from other types of mammals and/or patients with other types of ataxia so as to determine

whether other mutations associated with ataxia exist in the protein kinase C gene of such subjects.

(See page 6 of non-final Office Action mailed February 15, 2007.) However, the Examiner concludes that the outcome of such experimentation cannot be predicted. Applicants respectfully disagree.

It is submitted that the claimed invention is enabled by the specification as filed in view of the knowledge of one skilled in the art at the time of filing. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in a patent coupled with information known in the art without undue experimentation. With respect to what constitutes undue experimentation, the following factors are relevant: the breadth of the claims; the nature of the invention; the state of the prior art, the relative skill of those in the art; the predictability of the art; the amount of guidance provided; the presence of working examples; and the quantity of experimentation necessary. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) (stating "the key word is undue, not experimentation."). As further pointed out by the Federal Circuit, "... the question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of enablement must not be unduly extensive." *PPG Indus., Ind. v. Guardian Indus., Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The specification provides a detailed description of methods of identifying genetic mutations that are associated with ataxia in a human subject, as well as working examples describing the successful identification of several such genetic mutations. For example, as described in the specification, any method of obtaining reliable nucleic acid sequence data from a mammalian subject, such as a human exhibiting ataxia, may be utilized. (See specification at page 7, line 1, to page 8, line 12.)

As acknowledged by the Examiner, one of skill in the art could clearly practice the various techniques of co-segregation analysis described in the specification. Numerous methods are described for DNA sequencing and co-segregation analysis, all of which are well known and routine in the art at the time of filing. (See specification at page 8, line 13, to page 13, line 24.) The full sequence of SEQ ID NO:3 is provided in the specification along with exemplary primers, provided in TABLE 1 and TABLE 2, for PCR amplification and sequencing SEQ ID NO:3 from genomic DNA. Moreover, working examples are provided that describe the identification of several mutations that are associated with ataxia in human subjects (e.g., H101Y in Example 1, S119P and G128D in Example 2, and R41P, S361G, and R597S in Example 3) in accordance with the methods of the claimed invention.

As further acknowledged by the Examiner, it is clearly within the ability of one skilled in the art to identify differences between various sequences. Therefore, it is noted that adequate guidance is provided in the specification to enable one skilled in the art to determine whether a genetic mutation in SEQ ID NO:3 co-segregates with adult-onset cerebellar ataxia. As described in the specification, the term 'genetic mutation' is an alteration of the wild-type protein kinase C gamma (PRKCG) sequence deposited in GENBANK, provided as SEQ ID NO:3 that is not a recognized polymorphism (i.e., has a population frequency less than 1% in mammalian control subjects of the same species that do not exhibit ataxia). (See specification at page 5, lines 1-4.)

As further described in the specification, once a mutation is identified in a subject exhibiting adult onset cerebellar ataxia, co-segregation analysis is carried out to determine if the particular mutation in the PRKCG co-segregates with the presence of adult onset cerebellar ataxia symptoms in the subjects tested. (Specification at page 11, line 30, to page 12, line 1.)

The specification provides examples of various methods that can be used to perform co-segregation analysis including, but not limited to, single stranded conformation analysis

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(SSCA), denaturing gradient gel electrophoresis (DGGE), RNAse protection assays, hybridization with allele-specific oligonucleotides, allele-specific PCR, and restriction fragment length polymorphism (RFLP). (See specification at page 12, line 1, to page 13, line 24.)

Moreover, the specification also provides working examples of co-segregation analysis. For example, as described in Example 1, a study was done in which the presence of the H101Y mutation was found in ten subjects exhibiting ataxia and was not found in 192 normal control subjects. (See specification at page 25, lines 4-10.) As described in Example 2, the S119P mutation was found in three human subjects exhibiting ataxia, and was not found in 96 control subjects. (See specification at page 26, lines 5-17.)

Therefore, it is submitted that the specification provides adequate guidance for one of skill in the art to practice the method of the invention as claimed.

3. It Would Not Require Undue Experimentation to Practice the Claimed Invention

The Examiner has taken the view that it is unpredictable as to whether one of skill in the art could practice the invention of the instant claims.

Contrary to the Examiner's assertion, it is submitted that the routine nature of the screening for mutations that are associated with ataxia is entirely consistent with the holding in *Wands*. As stated in *Wands*, "[e]nablement is not precluded by some experimentation, such as *routine screening*." *Wands*, 858 F.2d at 736-37 (emphasis added). As further stated in *Wands*:

> [t]he determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

Wands, 858 F.2d at 736-737.

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As further evidence of the routine nature of the experimentation required to practice the claimed invention, in view of the guidance provided in the instant specification, applicants wish to point out that additional mutations in the protein kinase C gamma gene (SEQ ID NO:3) that co-segregate with ataxia have successfully been identified by others in the field. For example, Nolte, D., et al., *Movement Disorders 22*(2):265-267 (2007), provided as Attachment A in the Response filed by applicants on June 15, 2007, describes the identification of the mutation G63V in two human subjects exhibiting ataxia which was not detected in control chromosomes from 200 healthy control subjects. In addition, as summarized in TABLE 1 of Nolte et al., numerous other mutations that co-segregate with ataxia have been identified by others in the field.

The Examiner has characterized the field of the invention as "unpredictable;" however, as described above, the methods required to practice the claimed invention are used routinely by those of skill in the art to successfully identify genetic mutations. Moreover, as pointed out by the Federal Circuit, "[w]e do not imply that patent applicants in art areas currently denominated as 'unpredictable' must never be allowed generic claims encompassing more than the particular species disclosed in their specification." *In re Vaeck*, 947 F.2d (Fed. Cir. 1991).

Therefore, applying the *Wands* factors to the instant application, it is apparent that a reasonable correlation exists between the scope asserted in the claimed subject matter and the scope of guidance provided by the specification in view of the knowledge of those skilled in the art. Applicants respectfully request removal of this ground of rejection.

Election of Species Requirement

Applicants agree with the Examiner's assertion that Nolte et al. teach that their data "stress the necessity to include all exons of PRKCG in the analysis of ataxia patients." Consistent with the teachings of Nolte et al., applicants pointed out in their traversal of the Restriction Requirement, filed on September 28, 2007, that the Examiner incorrectly

characterized the sequences listed in Claims 43 and 44 as independent and distinct inventions. As evidenced in Nolte et al. (published in 2007, several years after applicants' effective filing date), additional mutations in the PKC gamma gene that alter the amino acid sequence are not limited to one particular exon, to which the Examiner has required restriction, but have been identified in various exons, including exon 1, exon 2, exon 4, exon 5, exon 10 and exon 18. Therefore, upon the allowance of generic Claim 1, from which Claims 43 and 44 depend, applicants respectfully request rejoinder and consideration of the additional exon sequences of human protein kinase C gamma gene listed in Claim 43.

CONCLUSION

In view of the foregoing, applicants submit that all of the pending claims are in condition for allowance and notification to this effect is respectfully requested.

Respectfully submitted,

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